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Abstract: OBJECTIVE: To assess changes in electrocochleographic (ECoG) responses following short-term suprathreshold electrical stimulation during cochlear implant (CI) telemetry in CI recipients. METHODS: Extracochlear ECoG recordings were conducted before and after intraoperative short-term suprathreshold electrical stimulation. Tone bursts at 500, 750, and 1000 Hz as well as clicks were used as acoustic stimuli. Changes of ECoG responses were correlated to calculated maximum electrical charge levels. RESULTS: Fourteen subjects were included. On average, no significant changes of ECoG responses occurred in the earliest postoperative phase; therefore, also following short-term suprathreshold electrical stimulation. However, one subject (S7) showed a decrease of ECoG responses. Neural as well as hair cell components of the ECoG signal were affected. On average, the maximum electrical charge level was 22 nC (range, 15-37 nC). In S7, the maximum electrical charge level was 17 nC. No correlations were found between maximum electrical charge levels and changes of ECoG signals. CONCLUSION: In a majority of cases, electrophysiological responses to acoustic stimuli remain unchanged in the earliest postoperative phase. However, deterioration of cochlear function occurs in this phase. Neural as well as hair cell components of the ECoG signal are affected. Such deterioration is not associated with unusually high electrical charge levels during CI telemetry. Overall, our results support the notion that an electrical charge applied at levels used in the clinical routine does not have an acute deleterious effect on cochlear function.

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Electrocochleographic Responses Before and After Short-Term Suprathreshold Electrical Stimulation in Human Cochlear Implant Recipients

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Objective: To assess changes in electrocochleographic (ECoG) responses following short-term suprathreshold electrical stimulation during cochlear implant (CI) telemetry in CI recipients.
Methods: Extracochlear ECoG recordings were conducted before and after intraoperative short-term suprathreshold electrical stimulation. Tone bursts at 500, 750, and 1000 Hz as well as clicks were used as acoustic stimuli. Changes of ECoG responses were correlated to calculated maximum electrical charge levels.
Results: Fourteen subjects were included. On average, no significant changes of ECoG responses occurred in the earliest postoperative phase; therefore, also following short-term suprathreshold electrical stimulation. However, one subject (S7) showed a decrease of ECoG responses. Neural as well as hair cell components of the ECoG signal were affected. On average, the maximum electrical charge level was 22 nC (range, 15–37 nC). In S7, the maximum electrical charge level was 17 nC. No correlations were found between maximum electrical charge levels and changes of ECoG signals.
Conclusion: In a majority of cases, electrophysiological responses to acoustic stimuli remain unchanged in the earliest postoperative phase. However, deterioration of cochlear function occurs in this phase. Neural as well as hair cell components of the ECoG signal are affected. Such deterioration is not associated with unusually high electrical charge levels during CI telemetry. Overall, our results support the notion that an electrical charge applied at levels used in the clinical routine does not have an acute deleterious effect on cochlear function. **Key Words:** Cochlear implant—Cochlear implantation—Electrical stimulation—Electrocochleography—Hearing preservation—Residual hearing.

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Preserving residual acoustic hearing is among the current frontiers in cochlear implant (CI) surgery and should be attempted in all CI recipients with residual hearing capacities (1,2). Preservation of residual hearing allows electric-acoustic stimulation (EAS) (3–5) in CI recipients with considerable residual hearing in the low frequencies and seems to lead to better speech understanding in the electric-only condition in conventional CI recipients (1,2).

Over the last years, refined surgical techniques and modern electrode designs have improved hearing conservation rates (6). However, to further improve hearing preservation rates, a better understanding of the mechanisms leading to partial or complete loss of residual hearing is crucial. This holds especially true for late-onset post-implantation hearing loss which occurs in about 20% of CI recipients (7–9). In such cases, even if hearing capacities are preserved up to 1 month after surgery, loss of residual hearing starts to progress to deafness slowly after a few months (7,9,10).

Kopelovich et al. (8) and Reiss et al. (11) have suggested that electrical stimulation itself may be responsible for this late-onset post-implantation hearing loss in EAS patients. They argued that excitotoxicity from EAS may cause hearing loss in a manner similar to noise-induced hearing loss (12). In experiments conducted on rat cochleotypic explants, acute high voltage electrical stimulation damaged dendrites of spiral ganglion neurons.

Electrocochleography (ECoG) as a method to assess cochlear function has been known for many years (13). As hair cells and the cochlear nerve contribute to the ECoG signal, information regarding the function of both components can be extracted (14–17). The ECoG signal consists of four different potentials: the cochlear microphonic (CM), the summating potential (SP), the

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auditory nerve neurophonic (ANN), and the compound action potential (CAP). The CM, SP, and ANN are part of the ongoing portion of the ECoG signal, which lasts for the duration of the sound stimulus (18). The CM primarily represents an outer hair cell response (19). The SP is predominantly correlate to the sustained depolarization of hair cell bodies, although neural components contribute to the signal as well (20,21). The ANN is the electrophysiological equivalent to phase-locked responses of auditory nerve fibers (22). The CAP, which is produced by synchronous neural firing, occurs at the onset and offset of sound stimuli and is not part of the ongoing portion of the ECoG signal. In ECoG recordings from the round window, a clear differentiation between hair cell and neural components is difficult, especially in the low frequencies and at high intensities (21). When low frequency, high intensity acoustic stimuli are used, the CAP is the only neural component of the ECoG response which can be assessed independently (21).

Immediately after insertion of the CI electrode, a first objective assessment of implant function and its physiological coupling to the auditory nerve (23) is routinely performed in many centers. Thereby suprathreshold electrical charge is applied and electrically evoked CAPs are measured by a bidirectional stimulating-recording system via the CI. This procedure is generally referred to as CI telemetry, but has manufacturer-specific names including Neural Response Telemetry (NRT) in Cochlear devices (Cochlear, Sydney, Australia), Neural Response Imaging (NRI) in Advanced Bionics devices (Advanced Bionics, Staefa, Switzerland), Auditory Nerve Response Telemetry (ART) in MED-EL devices (MED-EL, Innsbruck, Austria), or Neuro ECAP 1.0 Telemetry in Oticon Medical devices (Oticon Inc, Somerset, NJ).

In human CI recipients, ECoG has been used to assess changes in cochlear function during the insertion of the CI electrode (14,16,18,23–27). However, to our knowledge neither ECoG nor other methods have been used to investigate changes of cochlear function immediately after suprathreshold electrical stimulation in human CI recipients. Therefore, the aim of this study was to determine if immediately after intraoperative suprathreshold electrical stimulation changes in cochlear function were detectable by ECoG. Based on the findings of Kopelovich et al. (8), which described damage to dendrites of spiral ganglion neurons immediately after electrical stimulation, we hypothesized that if intraoperative suprathreshold electrical stimulation causes changes of cochlear electrophysiology, then the most likely finding would be a change in the neural contribution to the ECoG signal.

MATERIALS AND METHODS

All procedures were in accordance with the terms of the Ethical Committee of Zurich (KEK-ZH-Nr. 2013–0317) and the Helsinki Declaration. Before surgery, written informed consent was obtained for all subjects.

Surgery and Recording Setup

All subjects were implanted at the University Hospital of Zurich, Switzerland. For acoustic stimulation a sterilized foam insert earphone (Biologic Systems, Mundelein, IL) attached to a sound tube was placed in the outer ear canal. The presurgical recording setup further included two sterile disposable monopolar needle electrodes (Neurosign, Magstim Co., Wales, UK) placed on the contralateral preauricular area and the glabella. The surgical procedure is described in detail in our previous studies (25,18). Briefly, a standard transmastoid facial recess approach was performed. Then, either an anterior–inferior cochleostomy or a round window access was performed in concordance with soft surgical procedures. The CI electrode was inserted carefully and the insertion site sealed with periosteum. A monopolar needle electrode (Neurosign) was placed on the promontory as recording electrode and left in an unchanged position for all ECoG recordings. Impedance measurements were performed and if impedances were less than 10 kΩ for all electrodes, then baseline ECoG data were acquired. Afterwards, CI telemetry was performed. Following suprathreshold electrical stimulation, the ECoG recordings were repeated. Lastly, the recording electrode was removed and the wound was closed in layers.

ECoG Recordings

As described above, a probe fixed to the promontory was used as the active input for recordings (‘‘positive’’), a surface electrode on the contralateral preauricular region served as the return (‘‘negative’’), and the common was a surface electrode on the forehead (‘‘ground’’). Both, acoustic stimulation and recording were conducted using the Navigator Pro device and the AEP software, version 7.0.0, from Biologic Systems.

Phase alternating sinusoidal tones at 500, 750, and 1000 Hz as well as clicks were used as acoustic stimuli. Responses to 400 tone bursts or clicks were averaged. Tone bursts had two-cycle rise and fall times. The plateau phase was 10 cycles at 500 Hz, 15 cycles at 750 Hz, and 20 cycles at 1000 Hz. Sound pressure for ECoG recordings was 95 dB nHL at 500 Hz, 100 dB nHL at 750 Hz, and 1000 Hz, and 95 dB nHL for click stimuli. The recording window for tone bursts was 32 ms, starting 4 ms before stimulus presentation. For click stimuli, the recording window was 10.66 ms, starting 1 ms before stimulus presentation. The sampling rate was 8000 Hz for the 500 Hz, 750 Hz and click stimuli and 16,000 Hz for the 1000 Hz stimuli. The recording amplifier’s high pass and low pass filters were set at 10 and 3000 Hz for 500 and 750 Hz; 10 and 5000 Hz for 1000 Hz; and 10 and 1500 Hz for clicks. A threshold of 47.5 μV was selected for artifact rejection.

Data from the AEP software were exported using the AEP To ASCII software from Biologic Systems. For further postprocessing MATLAB (MathWorks Inc., Natick, MA) and GraphPad Prism V5.04 (GraphPad Software Inc., San Diego, CA) were used.

The average ECoG responses from condensation and rarefaction phases were stored separately. The difference curve was obtained by subtracting the average of the condensation from the average of the rarefaction phase, and the alternating curve summating both averages. A Fast Fourier transform (FFT) was applied to determine the spectrum for each difference and alternating curve.

To assess the neural contribution to the ECoG signal, the presence of a CAP in response to tone bursts and click stimuli was assessed visually in the alternating curve and its peak-to-peak amplitude was measured.

To assess the hair cell function, the ongoing ECoG response was analyzed. The sum of the response amplitude at the stimulus frequency (i.e., fundamental frequency or first harmonic) in the difference curve and at the frequency of the second harmonic in the alternating curve was defined as the amplitude of the ongoing ECoG response at the frequency of the acoustic stimulus. It has to be said that the ANN also contributes to the ongoing ECoG response and therefore the ongoing ECoG response probably is not a pure hair cell response. However, at high intensities the first and also second harmonic component of the ongoing ECoG response is clearly dominated by hair cell responses (21) which was the reason to use the ongoing ECoG response as metric to assess the hair cell function.

The main noise floor and its standard deviations were determined for each frequency from all bins within 50 Hz on each side, starting 50 Hz away from the peak of the assessed frequency. Validation criteria were met if the amplitude of the response exceeded the calculated noise floor + 3 standard deviations.

By adding the amplitudes of the ongoing ECoG responses at 500, 750, and 1000 Hz, a measure of hair cell function for the low frequencies—termed the ''low-frequency ECoG response''—was determined. A change of more than 3 dB in the low-frequency ECoG response was defined as relevant (26).

Electrical Stimulation

For each electrode, the maximum electrical stimulation level during CI telemetry, termed maximal probe current level (CL) in the Custom Sound EP for Cochlear devices and high clinical unit (CU) in the Soundwave Fitting Software for Advanced Bionics devices, was converted to electrical charge (nanoCoulombs). The following equations were used:

Cochlear Nucleus implants (CI-422, CI-522, CI-512):

$$\text{Current(microampere)} = 1.75 \times 100^{(\text{clinical units in CL}/255)} \quad (1)$$

$$\text{Charge (nanoCoulombs)} = (\text{microampere} \times \text{pulse width [ms]})/1000 \quad (2)$$

Advanced Bionics implants (HiFocus V):

$$\text{Charge(nanoCoulombs)} = \text{CU} \times 0.07786$$

For each subject, the maximum electrical charge was averaged over all electrodes.

Statistical Analysis

All statistical analyses were conducted with Stata Statistical Software (Release 13, StataCorp LP, College Station, TX). A *t* test for two dependent means was used to evaluate the difference between two mean values before and after CI telemetry. A significance level of 0.05 was chosen. A Pearson's correlation coefficient was used to measure the strength and direction of the relationship between two variables.

RESULTS

Fourteen subjects were included in this study. In S1, only recordings to acoustic click stimuli were performed. Mean age was 50 years (range, 20–71 yr). Eleven subjects were implanted with a Cochlear Nucleus device (one CI-422, six CI-522, and four CI-512). Three were implanted with an Advanced Bionics HiFocus V MidScala electrode. Surgeries were performed between May 2015 and August 2016. No complications occurred during surgery. Mean time between the last ECoG recording before electrical stimulation and the first ECoG recording after electrical stimulation was 14.6 minutes (range, 8–33 min). Subject demographics and electrophysiological data are summarized in Table 1.

Before electrical stimulation CAPs in response to acoustic click stimuli were detectable in 10 out of 14 subjects. The mean peak-to-peak amplitude was 1.3 uV (SD 1.0 uV). Mean change of the CAP amplitude after electrical stimulation was 0.01 uV (SD 0.5 uV, $t(9) = 0.04$, $p = 0.97$). Only S7 showed a loss of the CAP in response to the acoustic click (Fig. 1).

In response to 500, 750, and 1000 Hz tone bursts, at least one CAP was recorded in 11 out of 13 subjects before electrical stimulation. Subjects S8 and S11 showed no detectable CAP at any frequency. S4 showed

TABLE 1. *Subject demographics and electrophysiological data*

				CAP Response in the 1st ECoG Recording				
Subject	Age (y)	Cochlear-Implant	Time Between ECoG recordings (min)	Click Stimulus	500 Hz Tone Burst	750 Hz Tone Burst	1000 Hz Tone Burst	Low-Frequency ECoG Response in the 1st ECoG Recording
1	57	CI-522	13	Yes	NA	NA	NA	NA
2	54	HiFocus V	33	Yes	Yes	Yes	Yes	Yes
3	24	CI-522	11	Yes	Yes	Yes	Yes	Yes
4	56	CI-512	12	No	No	Yes	No	Yes
5	32	HiFocus V	19	Yes	Yes	Yes	Yes	Yes
6	65	CI-522	17	No	Yes	Yes	Yes	Yes
7	62	CI-422	12	Yes	Yes	Yes	Yes	Yes
8	61	CI-512	12	No	No	No	No	Yes
9	44	CI-512	13	Yes	Yes	Yes	Yes	Yes
10	71	CI-522	12	Yes	Yes	Yes	Yes	Yes
11	56	HiFocus V	8	No	No	No	No	Yes
12	61	CI-522	12	Yes	Yes	Yes	Yes	Yes
13	30	CI-522	13	Yes	Yes	Yes	Yes	Yes
14	20	CI-512	17	Yes	Yes	Yes	Yes	Yes

CAP indicates compound action potential; ECoG, electrocochleography; NA, not applicable.

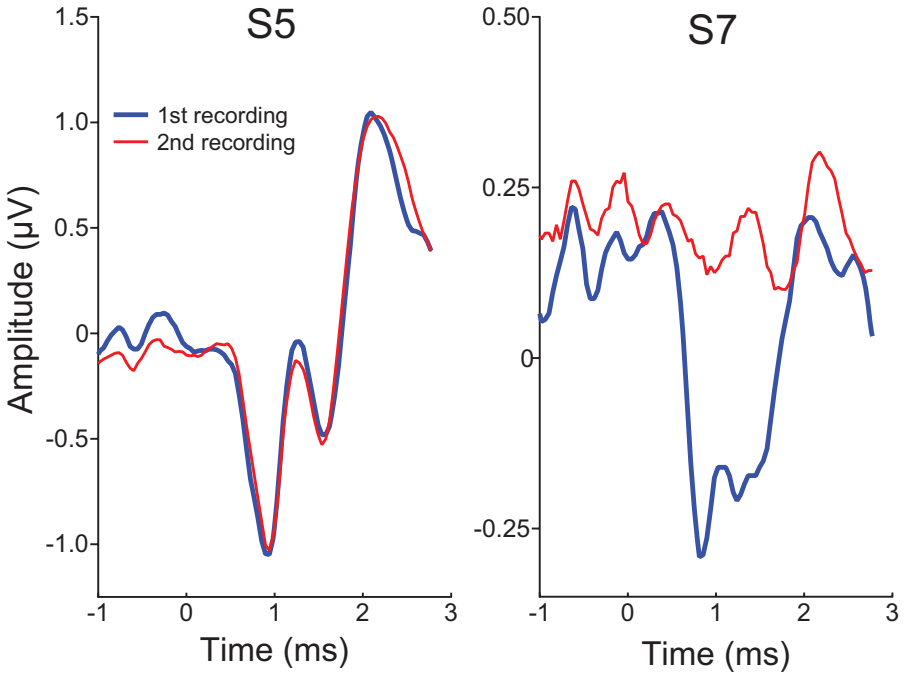

FIG. 1. CAPs in response to acoustic click stimuli. In S5, the CAP amplitude remained unchanged after electrical stimulation; in S7, the CAP was not detectable in the 2nd recording. CAP indicates compound action potential.

a small CAP at 750 Hz, but no CAP in response to 500 and 1000 Hz tone bursts. All other subjects had detectable CAPs at all three frequencies. All subjects except S7 showed unchanged CAPs in response to the low-frequency tone bursts after short-term suprathreshold electrical stimulation. While S7 displayed clear CAPs at all frequencies before electric stimulation, the CAP response decreased at 500 Hz and was completely absent at 750 and 1000 Hz following electrical stimulation (Fig. 2). The mean peak-to-peak amplitude before electrical stimulation was 4.1 uV at 500 Hz (SD 1.8 uV), 4.3 uV at 750 Hz (SD 2.4 uV), and 2.9 uV at 1000 Hz (SD

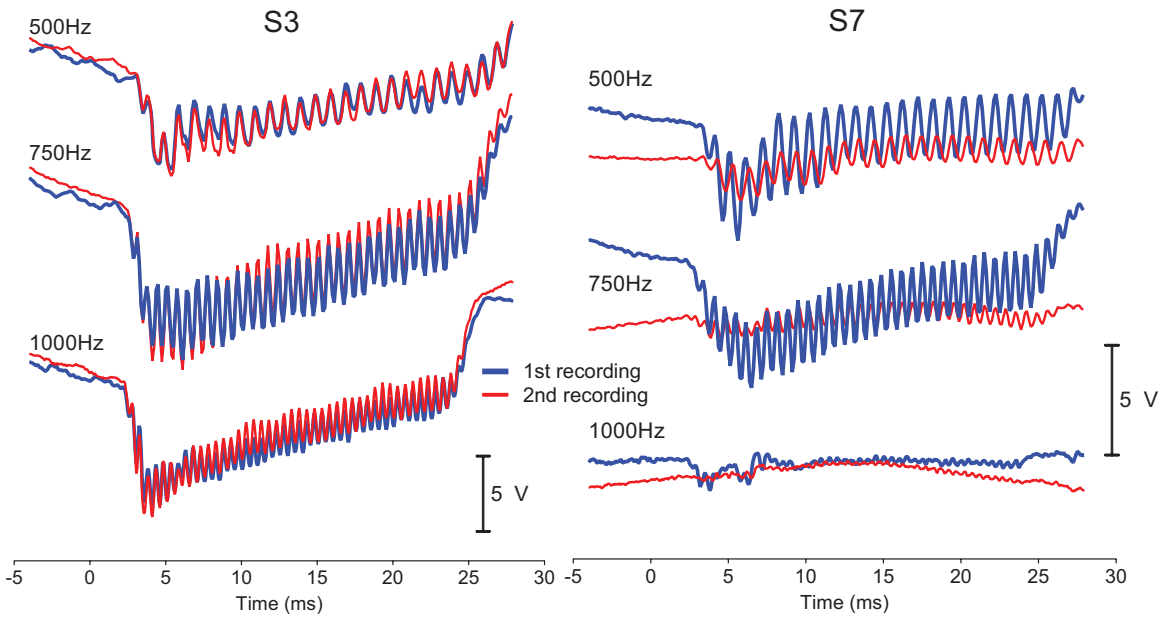

FIG. 2. CAPs in response to tone bursts at 500, 750, and 1000 Hz. The alternating curves are shown. S3 was chosen as an exemplary case. The CAP showed no or minimal change between both recordings. In S7, a decrease or loss of the CAP responses were detectable. CAP indicates compound action potential.

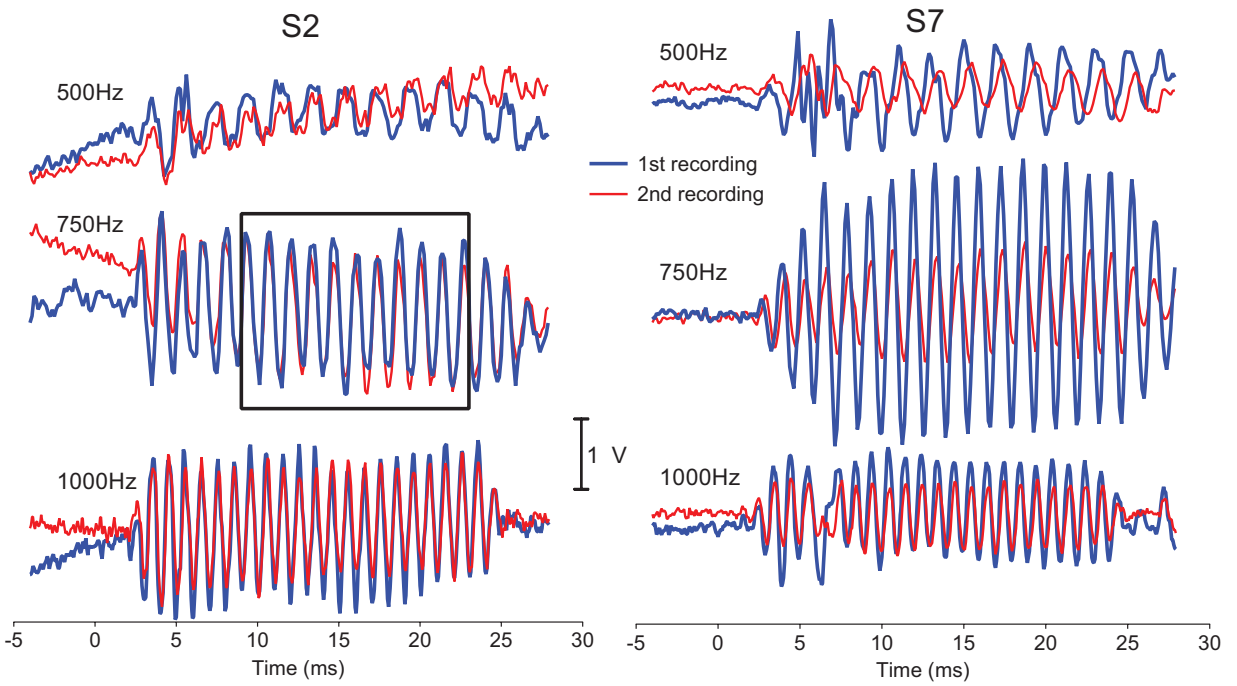

FIG. 3. Ongoing ECoG responses at 500, 750, and 1000 Hz. The difference curves before and after suprathreshold electrical stimulation are shown. The time window used for the assessment of the ongoing ECoG response is marked. The responses of S2 were chosen as examples for unchanged ongoing ECoG responses (mean change −1.8 dB). S7 showed a clear decrease of the ECoG response for all three frequencies (mean change −7 dB). ECoG indicates electrocochleographic.

2.0 uV). After electrical stimulation, the mean difference in the peak-to-peak amplitude was of −0.04 uV at 500 Hz (SD 1.3 uV, $t(9) = -0.08$, $p = 0.94$), −0.3 uV at 750 Hz (SD 2.0 uV, $t(10) = -0.43$, $p = 0.68$), and −0.1 uV at 1000 Hz (SD 0.7 uV, $t(9) = -0.25$, $p = 0.81$).

The mean low-frequency ECoG response amplitude before electrical stimulation was 33.5 dB re 0.1 uV (standard deviation 6.6 dB). The mean change after suprathreshold electrical stimulation was −0.3 dB (range, −7–2.9 dB, standard deviation [SD] 2.5 dB, $t(12) = -1$, $p = 0.34$). Only S7 showed a relevant change of the low-frequency ECoG response. The amplitude decreased by 7 dB after suprathreshold electrical stimulation (Fig. 3).

Maximum electrical charge during CI telemetry ranged from 15 to 37 nC (mean 22 nC). No correlations were found between maximum electrical charge and changes of the CAP responses to click stimuli ($r^2 = -0.1$) and the CAP responses to 500 Hz ($r^2 = 0.0002$), 750 Hz ($r^2 = 0.0003$), and 1000 Hz ($r^2 = 0.07$) tone bursts (Fig. 4). S7 had a maximum electrical charge level of 17 nC.

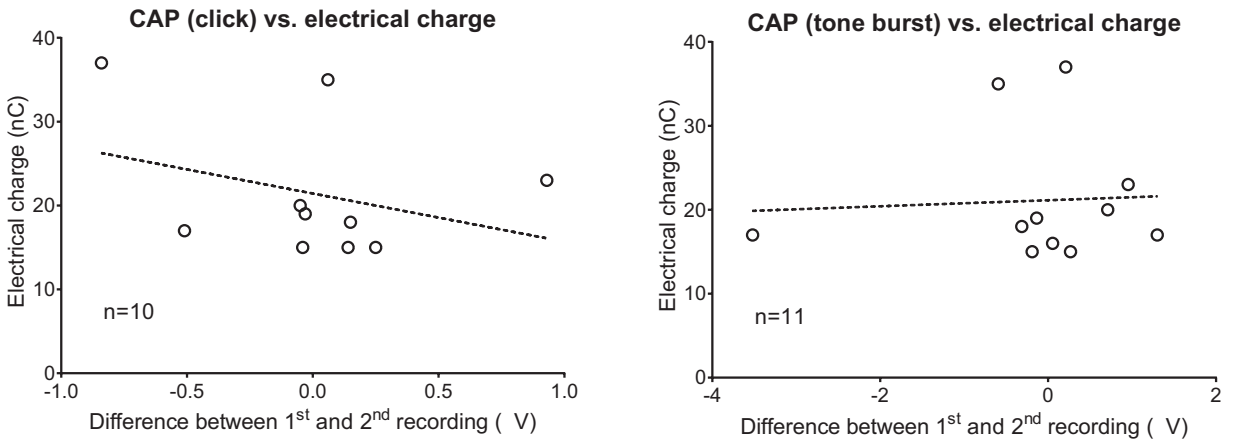

FIG. 4. No correlations were detectable between changes of the CAP and the electrical charge applied during intraoperative suprathreshold electrical stimulation. The correlation was assessed for the CAP in response to a click stimulus and the CAP in response to tone bursts. CAP indicates compound action potential.

DISCUSSION

Approximately, 20% of CI recipients experience a post-implantation hearing loss over the months following CI activation (7–9). The mechanism underlying this late-onset post-implantation hearing loss is still controversial. Recently, Kopelovich et al. (8) hypothesized that electrical stimulation may cause afferent cochlear innervation injury, which may contribute to hearing loss. In an effort to address their hypothesis, we conducted ECoG recordings following intraoperative suprathreshold electrical stimulation in human CI recipients.

The ability of spiral ganglion cells to survive long-term electrical stimulation was recognized early as being crucial for the success of cochlear prostheses. Therefore, several studies evaluated the effect of chronic cochlear implantation and intracochlear electrical stimulation on cochlear structures in animal models. The results suggested that apart from hair cell loss in close proximity to the implant, long-term electrical stimulation did not adversely affect residual auditory nerve elements or hair cells in normal hearing and deafened cats and kittens (28–32).

However, there is also a small but considerable amount of evidence proposing adverse impacts of high-intensity electrical stimulation (28,33). Kopelovich et al. (8) examined the consequences of excessive electrical stimulation on rat organotypic explants and found degeneration of spiral ganglion cell dendrites connected to inner hair cells without any detectable damage to the hair cells, a finding that shows remarkable similarity to glutamate-mediated ototoxicity.

Synapses formed by inner hair cells and afferent dendrites of spiral ganglion neurons use glutamate as their primary neurotransmitter (34). Apart from its rapid excitatory properties, when excessively released or inappropriately recycled, glutamate is well known for its neurotoxic potential. In the cochlea, noise trauma (35) and ischemia (36) have been shown to induce glutamate effluxes great enough to cause cochlear tissue damage. Consistent with Kopelovich's histological findings, the dominant excitotoxic lesion sites are type I afferent spiral ganglion neuron dendrites below inner hair cells, while hair cells themselves seem to be unaffected (37). Altogether, this led to the assumption that high intensity electrical stimulation may trigger glutamate effluxes sufficient to induce cochlear tissue damage in a similar way as noise does and thereby contribute to late-onset hearing loss in CI patients (8).

Based on this hypothesis, we expected that if acute high-charge electrical stimulation during intraoperative suprathreshold electrical stimulation caused detectable changes in cochlear function, then changes would show a decrease of the neural component to the ECoG response. Such reduced neural contribution could manifest itself in a reduction of the CAP amplitude (21). In the present study, only one subject (S7) showed such a reduction of the CAP response amplitude. Furthermore, statistical analyses revealed no significant group effects suggesting systematic changes of the CAP after short-term suprathreshold electrical stimulation.

Following electrical stimulation, S7 showed a decrease of the CAP amplitude at 500 Hz, and a complete loss of the CAPs in response to 750 and 1000 Hz tone bursts as well as click stimuli. However, a simultaneous decrease of the ongoing low-frequency ECoG response was detectable, suggesting also a deterioration of hair cell function. Furthermore, the maximum electrical charge in S7 was below the mean maximum electrical charge applied in the rest of the study population (17 nC versus 22 nC). Therefore, it seems unlikely that the loss of cochlear function is caused by electrical stimulation. Hypothetically, an increased sensitivity of cochlear structures to electrical stimulation in S7 is possible, although underlying mechanisms that could cause such an increased sensitivity are unknown. Still, in our view the loss of cochlear function in S7 was more likely triggered by trauma or injury to cochlear structures during insertion of the CI electrode array. If this holds true, then the fact that in S7 changes in ECoG responses appeared with a delay is an interesting finding and implies that previous studies (14,16,18,23–27) that assessed changes in ECoG responses only during and immediately after electrode insertion may have underestimated the influence of acute trauma during electrode insertion on post-implantation hearing loss. Such delayed deterioration of cochlear function could partially explain why changes in low-frequency ECoG recordings during surgery do not directly translate into postoperative hearing loss (27).

It has to be emphasized that all animal studies or studies using models of the inner ear that report cochlear damage following electrical stimulation used higher electrical charge levels over a longer stimulation period compared with this present study in human CI recipients. Kopelovich et al. (8) titrated the voltage level to the point where the first structural tissue damage in organotypic cultures occurred. This was the case for a charge level of 0.36 uC/phase, an order of magnitude greater than used clinically in CI recipients. Mean maximum electrical charge applied during suprathreshold electrical stimulation in the present study ranged from 0.015 to 0.037 nC/phase.

CONCLUSION

In a majority of cases, electrophysiological responses to acoustic stimuli remain unchanged in the earliest postoperative phase and after acute suprathreshold electrical stimulation. Still, deterioration of cochlear function occurs in this early phase but underlying mechanisms independent from the electrical stimulation seem more likely. Overall, our results support the notion that electrical charge applied at levels used in the clinical routine does not have an acute deleterious effect on cochlear function. The present study allows no conclusions to be drawn regarding the influence of chronic electrical

stimulation on preservation of cochlear structures and hearing preservation.

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